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To: SUSAN LEWIS PM 21
Product Manager
Registration Division (H7505C)

From: Douglas J. Urban, Acting Chief
Ecological Effects Branch/EFED (H7507C)

Attached, please find the EEB review of...

Reg./File # : 284055
Chemical Name : BENOMYL
Type Product :
Product Name :
Company Name : DUPONT
Purpose : REVIEW INFORMATION ON ADVERSE EFFECTS
RELATED TO BENOMYL

Action Code : 405 Date Due : 10-31-92
Reviewer : RICK PETRIE Date In EEB: 10-14-92

EEB Guideline/MRID Summary Table: The review in this package contains an evaluation of the following:

GDLN NO	MRID NO	CAT	GDLN NO	MRID NO	CAT	GDLN NO	MRID NO	CAT
71-1(A)			72-2(A)			72-7(A)		
71-1(B)			72-2(B)			72-7(B)		
71-2(A)			72-3(A)			122-1(A)		
71-2(B)			72-3(B)			122-1(B)		
71-3			72-3(C)			122-2		
71-4(A)			72-3(D)			123-1(A)		
71-4(B)			72-3(E)			123-1(B)		
71-5(A)			72-3(F)			123-2		
71-5(B)			72-4(A)			124-1		
72-1(A)			72-4(B)			124-2		
72-1(B)			72-5			141-1		
72-1(C)			72-6			141-2		
72-1(D)						141-5		

Y=Acceptable (Study satisfied Guideline)/Concur
P=Partial (Study partially fulfilled Guideline but additional information is needed)
S=Supplemental (Study provided useful information but Guideline was not satisfied)
N=Unacceptable (Study was rejected)/Nonconcur



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

284055

MEMORANDUM

NOV 10 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Review of Information From DuPont Regarding Benlate
DF Testing

FROM: Douglas J. Urban, Acting Chief
Ecological Effects Branch
Environmental Fate and Effects Division (H7507C) 11/9/92

TO: Susan Lewis, PM-21
Fungicide/Herbicide Branch
Registration Division (H7505C)

The Ecological Effects Branch (EEB) has reviewed the DuPont information provided in response to a letter from Doug Campt to Rick Holt of DuPont dated 9/04/92 and in response to information requested by OPP scientists in a September 17, 1992 meeting with DuPont scientists at EPA. The information package on Benlate 50DF testing included: copies of slides presented on Sept. 17th and copies of original medical reports (Attachments A to E). Also included in the package is a request/proposal for research funding plus unpublished, non-peer reviewed research from Dr. R. H. Biggs, Professor Emeritus with the University of Florida (FAX from DuPont Chem. Co. to Carl Grable of Registration Division dated Oct. 2, 1992). The EEB has been asked to assess the adequacy of the phytotoxicity testing on Benlate 50 DF to date.

TYPES OF INFORMATION SUBMITTED

The EEB was unable to conduct a formal data evaluation (DER) for any of the information submitted by DuPont because only summaries (slides) of test results were provided. No test protocols or raw data were provided. From the limited information submitted in Attachment A (Root Cause Analysis), it appears that DuPont has conducted a wide array of plant toxicity tests including whole plant bioassays, root bag bioassays, Lemna gibba hydroponic studies, general herbicide screening studies, immunoassay screens for herbicide contaminants, and limited field studies. Rates ranging from maximum label rate to 10X the maximum label rate were used in some of the tests. In most studies, study duration ranged

from 6 to 14 days, with the exception of a limited number of ornamental field studies in Bradenton, FL. that involved 3 to 6 applications and observations at 14 day intervals. It appears that the majority of applications were soil drenches which would place most of the chemical in the root zone.

A review of human health incident reports in Attachment B provided the following phytotoxicity information: peaches, apples, plums and grapevines injured in Cleveland, GA.; squash and papayas injured in Naranjitos, PR.; blueberry bushes injured in Waldo, FL.; ornamental plants (species not identified) injured in hotel lobby display (DuPont representatives confirmed that the symptoms of phytotoxicity were similar to those observed in other Benlate DF damage claims); orchids injured in Ft. Lauderdale, FL. Symptoms included plants turning yellow and dying.

Attachment C of the DuPont submission contained a published pamphlet from the University of Florida titled "Production Management and Fungicide Alternatives to Benlate on Ornamental Crops", authors Ann Chase, Tom Yeager, Gary Simone and Mike Evans. This pamphlet gives the ornamental crop growers a list of plant injury symptoms induced by Benlate DF or Tersan DF formulations. The symptoms described such as plant stunting, smaller than normal twisted leaves occurring in rosettes, leaves with chlorosis or yellow appearance, leaf tips or margins necrotic and turned down (cupped), leaf drop, and roots that appear darker than normal a few inches behind the growing tip. Some of these symptoms are similar to symptoms of sulfonylurea herbicide injury, as described in the literature.

The University of Florida information package from DuPont to C. Grable is clearly marked with the following statement on each page: "The scientific contents of this document have not been reviewed and the contents do not necessarily represent scientific conclusions that can be supported by the University of Florida's Institute of Food and Agricultural Sciences." A "preliminary draft" paper titled "Cucumber Bioassay For Phytotoxic Residues In Greenhouses, Nurseries, And Other Cropping Systems" by R.H. Biggs, Dept. of Horticultural Sciences, University of Florida, Gainesville was submitted. Dr. Robert H. Biggs is a Professor (Biochemist) and has served with the University of Florida for 35 years. The EEB cannot conduct a formal data evaluation (DER) of this data because of it's "preliminary draft" status. In the information presented, Dr. Biggs suggests that the following plants are more sensitive to Benlate DF injury than others: peanuts, onions, beans, grasses, crucifers, tomatoes, corn, peas, marigolds, peppers, cucumbers, asparagus and the perennials American elm, sycamore, buckthorn, and pecan trees. Dr. Biggs claims that he has replicated the phytotoxicity observed in the field using a cucumber bioassay test. Dr. Biggs suspects that Benlate DF degrades to dibutyl urea which

causes sulfonylurea type effects on plants.

An EPA literature search was conducted by Health Effects Division of OPP to identify published literature regarding the phytotoxic effects of benomyl, Benlate DF or Tersan DF, and the Benlate DF degradates MBC (methyl-2-benimidazolecarbamate), DBU (Dibutyl urea), and BIC (butylisocyanate). No plant phytotoxicity studies were found for these compounds in the literature.

ASSESSMENT OF INFORMATION SUBMITTED

DUPONT INFORMATION- A sophisticated "root cause analysis" was conducted to determine the cause of the extensive plant phytotoxicity that resulted in over 1850 claims for damages by growers, nurserymen, and nursery/greenhouse customers. DuPont conducted chemical and bioassay tests on 76 opened and 4000 unopened boxes of Benlate DF in an effort to identify the cause of the extensive phytotoxicity. The 76 opened bags were bags of Benomyl DF actually used by growers that resulted in crop injury. The bioassay tests were mostly 14 days in duration and were conducted with the annual plants tomato and petunia. Only one of the Benlate DF samples caused rapid plant death when applied to bioassay plants. This one sample contained very high levels of simazine herbicide. DuPont was unable to explain how the simazine was introduced into the Benlate DF sample as no simazine is produced at the Benlate DF manufacturing facility. Suspecting chemical contamination by the ALS (aminolactate synthase) inhibiting herbicides, the sulfonylureas and imazidolinones, immunoassay tests were conducted on the 4076 samples plus 13 soil samples from Florida field complaints. No ALS inhibiting herbicides were found in any samples down to the 5 to 20 ppb level of detection.

Being unable to detect the presence of a herbicide contaminant in Benlate DF, DuPont focused further research on Benlate DF degradates. Degradates include MBC, DBU, and BIC mentioned above. In bioassay tests where Benlate DF samples were spiked with various concentrations of dibutyl urea (DBU - a degradate of Benlate DF that can cause plant phytotoxicity), DuPont concluded that DBU can be phytotoxic when levels exceed 3%. More than 600 unopened boxes of Benlate DF were sampled for DBU. The majority of the samples contained less than 1%, however, the following sample numbers contained >1% DBU: No. 33 - 1.31 to 1.44%, No. 52 - 1.21 to 1.26%, No. 54 - 9.75 to 10.19%, No. 55 - 10.87 to 13.19%, No. 57 - 9.38 to 10.64%, No. 66 - 7.04 to 7.20%. In a 12 day Benlate DF drench study (Study No. 2177), a Benlate DF sample spiked with 10% DBU caused 80% stunting and marginal leaf burn on tomato. A greater than 25% adverse growth effect (hormonal and leaf burn) on petunia was observed with 7% (30% injury) DBU spiked Benomyl DF. A greater than 25% adverse growth effect in the form of stunted plants and chlorosis/marginal leaf burn occurred on tomato with DBU spiked concentrations of 3% (30% injury), 5% (30% injury), and 7% (60%

injury). High rate drench treatments of DBU spiked Benlate DF to woody ornamental plants in Bradenton, FL. failed to result in significant plant injury using drench treatments every 14 days for 12 weeks. Drench plus 2 foliar applications to petunias in Bradenton did result in 6 - 13% injury in a 5 day study at the maximum rate (drench only) and non-significant injury in a 12 day study (drench and 2 foliar treatments). At a 5X rate, root injury ranged from 20 - 43% and at a 10X rate injury to petunias ranged from 40 - 67%. Based on the fact that some of the Benlate DF samples contained levels of DBU that exceeded 3%, and that Benlate DF samples spiked with >3% DBU caused phytotoxicity to the bioassay plants tomato and petunia, there is evidence to suggest that some of the reported phytotoxicity incidents may have resulted from Benlate DF packages that contained >3% DBU.

No information regarding the phytotoxicity of the degradates MBC or BIC was provided. In the 09/17/92 meeting at the EPA with DuPont, the DuPont representatives stated that BIC phytotoxicity studies are ongoing.

DuPont has concluded that they do not know what caused the 1800+ cases of phytotoxicity and have been unable to replicate the effects in the laboratory using bio-assay plants at typical use rates. Only Benlate DF samples spiked with >3% DBU resulted in plant phytotoxicity in the greenhouse. DuPont was not clear as to whether or not the DBU induced injury symptoms were similar to those that occurred in the field (1800+ incidents). Very limited information was provided by DuPont regarding the plants injured, symptomology of injury observed, number of days from application to plant death, and if damages were confined to the treated field.

UNIVERSITY OF FLORIDA INFORMATION - Dr. Biggs cucumber bioassay research indicates that a combination of two Benlate DF degradates MBC and BIC, in combination with enhanced plant uptake due to something in the DF formulation results in short term phytotoxicity under high light, temperature, and humidity conditions. Dr. Biggs suspects that Benlate DF degrades to MBC which in turn degrades to DBU and BIC. Upon uptake by the plant, DBU produces sulfonylurea-type injury. Dr. Biggs suspects that BIC and MBC are also phytotoxic compounds. Phytotoxic effects include dwarfism, chlorosis, reproductive failure, limited root damage, brittleness, and varying degrees of leaf damage. Dr. Biggs reported that the benomyl DF formulation is more volatile than the WP formulation and produces more volatile anilines and BIC than the WP. Dr. Bigg's cucumber bioassay tests run for 60 to 70 days, long enough to evaluate reproductive effects. Dr. Bigg's research to date appears to be a series of problem solving tests looking at an array of possible contaminants (other herbicides such as picloram) and ways to reduce existing contamination in greenhouses such as the use of activated charcoal.

CONCLUSIONS:

The scientific validity of the information submitted cannot be assessed without raw data and test protocols. It is our understanding that the volume of raw data associated with the DuPont studies would be extensive and would take many months, possibly a year, to review. The University of Florida information is mostly summary data that has not been peer reviewed.

The DuPont "root cause analysis" was conducted using a scientific hypotheses approach and represented a major effort to determine the cause of plant phytotoxicity that occurred in over 1800 incidents. The summaries of DuPont plant tests to date indicate that the plant phytotoxicity observed in greenhouses and fields could not be replicated by DuPont, even when using samples of the same bags used by the growers that reported injury. DuPont applied up to 10X the normal application rate with minimal effects on plant growth. Most of the DuPont bioassays were of limited duration (14 days or less) and were conducted with tomato and petunia. Studies of longer duration (for the entire plant life cycle), application to plant foliage at all stages of plant growth, and different bioassay plants may have resulted in higher levels of phytotoxicity. However, DuPont has concluded that the phytotoxicity that occurred from use of the 2 pound pack of Benlate DF was not likely caused by a herbicide contaminant, product misuse, soil type, fertility practices, tank mix combinations, or Benlate DF degradates.

Phytotoxicity induced by Benlate DF degradates MBC, DBU and BIC is still an issue and will require further analysis. DuPont is currently conducting phytotoxicity studies on BIC. Samples of Benlate DF spiked with the degradate DBU resulted in plant phytotoxicity when concentrations exceeded 3%, however, most of the 600 off-the-shelf samples of the 2 pound package of Benlate DF failed to contain >1% DBU. It was unclear as to whether or not these 600 samples were a subset of the 4076 samples or if they were an additional 600 samples. Six samples did, however, contained >1% DBU. The EEB would like to see the specific bioassay results for each of the sample numbers identified as having > 1% DBU (No.s 33, 52, 54, 55, 57, and 66 listed under ASSESSMENT OF INFORMATION SUBMITTED) above. Benlate DF with greater than 3% DBU may have induced plant phytotoxicity in Benlate DF incidents.

The detection of ALS inhibiting herbicides in Benlate DF samples is limited by current limits of analytical detection of 5 to 20 ppb. Some sulfonylurea herbicides kill plants at 50 ppt and can adversely affect plant growth as low as 10 ppt. The ALS herbicides may be in test samples but not analytically detectible. Further bioassay tests might include an analysis of the most sensitive plant species, foliar applications with observations for the entire life cycle of the plant(s), and applications of Benlate DF at different growth stages (seed germination and emergence,

vegetative vigor, reproductive stages, post reproductive stages).

The University of Florida information submitted provided descriptions of the types of phytotoxic effects that occurred in nurseries and greenhouses treated with Benlate DF or Tersan DF. These symptoms of adverse plant effects are an important clue to the identity of the chemical(s) causing the adverse effects. Classes of herbicides, and even individual herbicides, can be identified based on their mode of action and phytotoxic effects. Dr. Robert H. Biggs of the University of Florida has observed Benlate DF induced phytotoxicity in Florida plant nurseries and groves and has identified what he considers the most sensitive plants. The information provided regarding Dr. Bigg's research is non-published and, therefore, not peer reviewed. However, the DuPont information is also non-published and not peer reviewed. Dr. Biggs selected the cucumber plant for his bioassay experiments. Dr. Biggs states in his report that he has replicated the same adverse plant effects he saw in the field in his greenhouse cucumber bioassays. In some experiments, Dr. Biggs observed the cucumber plants through their entire life cycle, 60 to 70 days to yield. DuPont has not conducted full life cycle studies on plants to our knowledge. Dr. Biggs has compared biological effects for the WP-50 formulation vs the DF-50 formulation and has noted more BIC and volatile anilines at high light, humidity, and temperature conditions for the DF-50 formulation. Dr. Biggs suspects that the degradates MBC, BIC, and DBU are all phytotoxic to plants. The Dr. Biggs research appears to be heading in the right direction toward identifying the compounds responsible for Benlate DF phytotoxicity.

The exact cause of the 1800+ cases of plant phytotoxicity has not yet been determined by DuPont or in independent University testing. If we pursue the cause of the phytotoxicity further, the EEB suggests that we provide the EPA Corvallis Laboratory with funding to coordinate University efforts to determine the status of ongoing research. Dr. Biggs and his colleagues Dr. M. Zabik at Michigan State University and Dr. Bushwaz at the University of Maine should be consulted further.

A review of incident data may shed some light on the most sensitive plants, phytotoxic symptoms, rates of application, etc., however, this effort would be very resource intensive. The EEB estimates 1/2 person year to review and summarize the 1800+ incident reports.

If you have any questions regarding this memorandum, please contact Richard Petrie @305-7358, CM-2 (Room 1030L).